Breathing patterns in patients with a Fontan circulation exposed to high altitude

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“ONDERGETEKENDE

Janneke Jolande Schot,

bevestigt hierbij dat de onderhavige verhandeling mag worden geraadpleegd en vrij mag worden gefotokopieerd. Bij het citeren moet steeds de titel en de auteur van de verhandeling worden vermeld.”

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ABSTRACT

Aim: To study the effect of simulated acute normobaric hypoxia on the breathing pattern of patients with a Fontan circulation (PwF) during exercise compared to a healthy control group.

Methods: This study included 23 PwF and 33 healthy controls between 8-40 years old. Median age 20, interquartile range [12:26]. Participants performed two cardiopulmonary exercise tests (CPET) on a cycle ergometer. One CPET was performed at sea level, the other CPET in a hypoxic tent at a simulated altitude of approximately 2500 metre above sea level. Outcome measures were respiratory minute ventilation, tidal volume, breathing frequency, ventilatory efficiency, ventilatory drive, minute ventilation per Watt and the rapid shallow breathing index. Measurements were compared in both conditions at four timepoints: at rest, ventilatory anaerobic threshold, respiratory compensation point, and peak exercise. Mann-Whitney U test and Wilcoxon signed-ranks test were used for statistical analysis.

Results: Statistically significant differences ($P<0.05$) were found in respiratory minute ventilation, tidal volume and breathing frequency between groups at altitude. Ventilatory efficiency, ventilatory drive and the rapid shallow breathing index showed significant higher values in PwF in both conditions.

Conclusion: A more rapid, shallow breathing pattern occurred in PwF during exercise when exposed to acute normobaric hypoxia compared to healthy controls.

Clinical Relevance : To overcome the less efficient rapid shallow breathing pattern, PwF might explore the possibilities of respiratory muscle training. This might be useful to improve ventilatory efficiency before high altitude exposure.

Keywords: Fontan, breathing patterns, hypoxia, cardiopulmonary exercise test, univentricular heart disease

1. INTRODUCTION

In the Netherlands, there are approximately 65.000 people living with a congenital heart disease (CHD) (1). There is an incidence of 71 per 10.000 living new-borns who are born with a congenital heart disease (1). This results in 1250 new-borns with a CHD each year (1). A distinction can be made between cyanotic and non-cyanotic CHD. A rare but very serious cyanotic CHD is when a child is born with only one functional ventricle (2). In 1971, F. Fontan described a surgical repair to overcome this disease which enables a univentricular circulation (3,4). The premise of the Fontan surgery is to separate the systemic venous and pulmonary circulations (2,4).

As a result of multifactorial processes, patients with a Fontan circulation (PwF) have a severe decline in the cardiorespiratory response to exercise resulting in a reduced exercise capacity (3). It is known that not only cardiac factors but also pulmonary factors play a role in this limitation, affecting breathing patterns (3). In PwF, higher values for respiratory minute ventilation (V_E), seem to be more driven by a significantly higher breathing frequency (B_f) than by a higher tidal volume (V_T) at peak exercise (5). This results in ventilatory inefficiency and higher dyspnoea sensations compared to healthy people (5). It is known that PwF have a deterioration in gas exchange, caused by a reduced lung volume, restrictive ventilatory defects and a non-pulsatile pulmonary blood flow (5–8).

Although PwF function well in daily life, they would also like to participate in activities such as adventure sports, recreation at high altitude and airplane travel (9). However, oxygen levels in the ambient air decrease when ascending. At a certain altitude, these levels are sub-optimal for humans and the human body needs to respond to these hypoxic changes (10). In the first five minutes when healthy subjects are exposed to hypoxia, ventilatory changes occur to prevent hypoxemia (11). The breathing pattern changes due to an increase of the breathing frequency and the tidal volume, causing an increased respiratory minute ventilation (11,12). This is called the hypoxic ventilatory response (10,13).

PwF experience dyspnoea sensations during airplane flight or during high altitude recreation. They often come to their health care providers with questions about their safety and health hazards regarding recreation at high altitude. It is hypothesised that there are differences in the hypoxic ventilatory responses of PwF during exercise compared to healthy controls. It is expected that a more rapid, shallow breathing pattern occurs in PwF during exercise when exposed to high altitude compared to healthy controls. This might cause the severe dyspnoea sensations of PwF at altitude. To validate this hypothesis and to be able to give proper answers and advises to these questions, there is a need to study the breathing patterns of PwF exposed to hypoxia.

Therefore, the primary objective is to study the effect of simulated acute normobaric hypoxia on the breathing patterns of PwF during exercise compared to a healthy control group.

The secondary objective is to study the effect of simulated acute normobaric hypoxia on the ventilatory efficiency (V_E/VO_2) and ventilatory drive (V_E/VCO_2) of PwF during exercise compared to a healthy control group. If a rapid shallow breathing pattern occurs, a low ventilatory efficiency is expected in PwF.

2. METHODS

This study is part of the HYPOXIA study which explores the hemodynamic and pulmonary effects during exercise at acute high altitude in patients with complex congenital heart disease. The current study intends to investigate breathing patterns of PwF during acute high altitude exposure with an observational cross-sectional controlled trial. Measurements were performed between October 2017 and June 2018 in the Utrecht Medical Centre Utrecht (UMCU), Wilhelmina Children's Hospital (WKZ) at the Child Development & Exercise Centre. The medical ethical research committee of the UMCU has approved the HYPOXIA study (NL56759.041.16).

This study included 23 PwF and 33 controls. To be eligible, participants had to be between 8 and 40 years old, had to be free from pulmonary obstructive disease (asthma or chronic obstructive pulmonary disease) and needed to be physically and mentally able to perform a cardiopulmonary exercise test (CPET). PwF were included if they were known to have univentricular heart disease and had undergone the Fontan procedure. Controls were eligible if they did not have a history of cardiovascular disorders. Participants who had undergone the Fontan procedure were approached via the paediatric cardiology department of the WKZ and the National Patient Association; healthy controls were recruited via a personal network of the researchers. All participants gave written informed consent.

Participants performed two CPETs in different conditions: one test was performed at sea level, the other was performed in a hypoxic tent (CAT-430^{TM} Walk-In Tent, Boulder, USA) at a simulated 2500 metre above sea level. In the hypoxic chamber, there was a gas mixture of ~15% oxygen and ~85% nitrogen, supplied by two generators (Hypoxic Everest Summit II Generator, BLM Altitude, Hoofddorp, The Netherlands). Each participant was randomly designated to the first condition: sea level or simulated altitude. This to prevent results being influenced by getting habituated to the test. To prevent results being influenced by fatigue, the second test was performed within three months after the first test but after at least two rest days.

The CPET was performed using an electronically braked upright cycle ergometer (Lode Corrival, Groningen, The Netherlands). Breath-by-breath analysis was done using a face mask with a flow meter (Hans Rudolph Inc, USA), which was calibrated with a metabolic cart (Geratherm, Bad Kissingen, Germany). The CPETs were performed following the Godfrey protocol (14). The test was terminated when the participant was unable to make at least 60 repetitions per minute, despite strong verbal encouragements of the physiologist, or due to safety reasons.

All outcome measures in both groups were retrieved by using a breath-by-breath analysis system during the CPET. The primary endpoints of this study were respiratory minute ventilation, tidal volume and the breathing frequency. The measurements were noted in both conditions at four time points: at rest, at the ventilatory anaerobic threshold (VAT), at the respiratory compensation point (RCP), and at peak exercise. Secondary study parameters were ventilatory efficiency (V_E/VO_2) and ventilatory drive (V_E/VCO_2). These measurements were also noted in both conditions at the four time points.

The rapid shallow breathing index (RSBI) was calculated in both conditions at the four timepoints. The RSBI is defined as the ratio of breathing frequency to tidal volume (B_f / V_T) in breath/minute/litre (15,16). Minute ventilation per Watt (V_E/Watt) was calculated by dividing the respiratory minute ventilation by the wattage in both conditions at VAT, RCP and peak exercise. A measure to describe ventilatory response to exercise, the slope of the regression line relating carbon dioxide output and respiratory minute ventilation (V_E/VCO_2-slope), was calculated (17,18).

Baseline characteristics were recorded: age, gender, total body mass, height, body mass index (BMI) and the New York Heart Association Classification (NYHA-class). The NYHA-class classifies the extent of heart failure in terms of how much a person is limited during physical activity. A NYHA-class of I means no limitation of physical activity, a NYHA-class of IV means unable to carry out any physical activity without discomfort (19).

2.1 Statistical methods

All data were checked on outliers, data-entry errors and missing data. The distributions of all outcome measures were tested using the Shapiro-Wilk test and QQ-plots. Continuous baseline characteristics were expressed as median [interquartile range]. To compare outcome measures between groups, the non-parametric Mann-Whitney U test was used since outcome measures after data transformation were not normally distributed. To compare outcome measures within groups, the non-parametric Wilcoxon signed-ranks test was performed. Significance level was set at $p<0.05$. All data analysis was performed in IBM SPSS statistics (version 24).

3. RESULTS

In total, 56 children and adults were included in the analysis (median age 20) of whom 23 PwF. Baseline characteristics of the participants are summarized in Table1.

Table 1: Baseline Characteristics.

Total (N=56)		Patients with a Fontan circulation (N=23)	Controls (N=33)	P-value[a]
Gender (male)		N= 15	N= 21	n.a.
Age (years)		15 [11 ; 25]	21 [14 ; 27]	0.166
Height (cm)		157 [143 ; 173]	175 [165 ; 183]	0.002*
Body Mass (kg)		48 [32 ; 65]	67 [52 ; 78]	0.009*
BMI (kg/m^2)		18 [16 ; 22]	21 [19 ; 24]	0.060
NYHA-class	I	N= 15	n.a.	n.a.
	II	N= 8		
	III	N= 0		
	IV	N= 0		

*Scores are presented as medians [interquartile range]; n.a. not applicable; *=P<0.05*
[a] *Comparing the groups with a two-sided Mann-Whitney U test.*

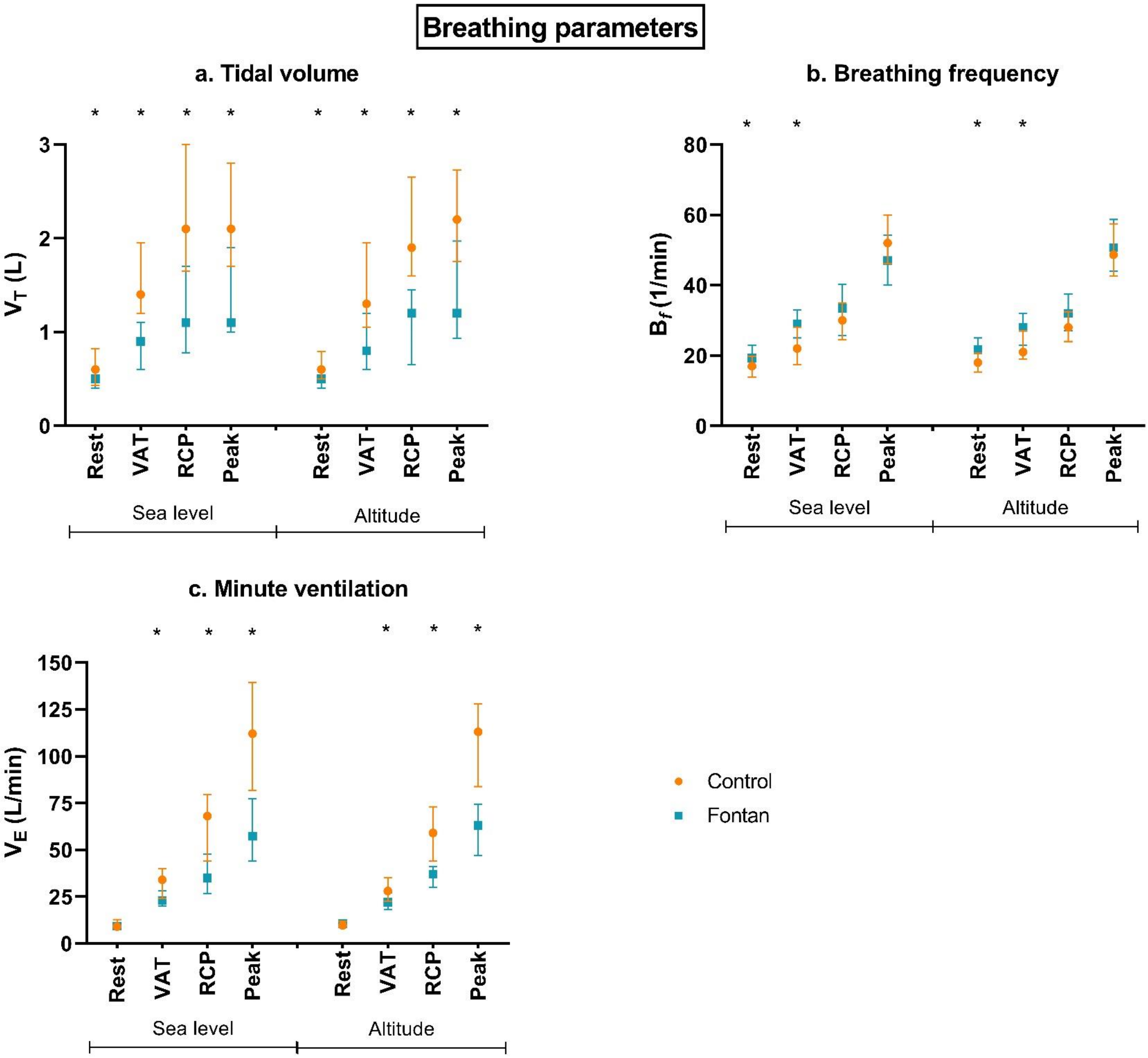
Primary analysis showed that there was a statistically significant difference in respiratory minute ventilation between groups at sea level as well as at simulated 2500m during the test at the different time points (Figure 1c). At VAT, RCP and peak exercise, the respiratory minute ventilation of PwF was lower. In both conditions, this difference could be partially described by a significantly lower tidal volume over all timepoints, see Figure 1a. Breathing frequency showed significant higher values at rest and VAT in both conditions, see Figure 1b. Ventilatory efficiency as well as ventilatory drive and V_E/VCO_2-slope showed significant higher values in PwF at all timepoints in both conditions compared to healthy controls (Figure 2).

For secondary analysis, the rapid shallow breathing index (RSBI) was calculated. This parameter showed statistically higher values for PwF at all timepoints in both conditions, which shows that PwF need more breaths per minute to inhale one litre of air compared to healthy controls (Figure 3a).

In addition, PwF had statistically significant higher values for ventilatory drive at altitude compared to sea level at VAT, RCP and Peak exercise (Figure 4d). Ventilatory efficiency only showed a statistically significant higher value at VAT (Figure 4e). Respiratory minute ventilation and breathing frequency did not show any relevant significant difference between the tests at altitude compared to sea level in PwF except during rest (Figure 4a-c). To correct for workload, the minute ventilation per Watt was calculated (V_E/Watt). This ratio showed a statistically significant greater values at altitude at peak exercise compared to sea level in PwF (Figure 3b).

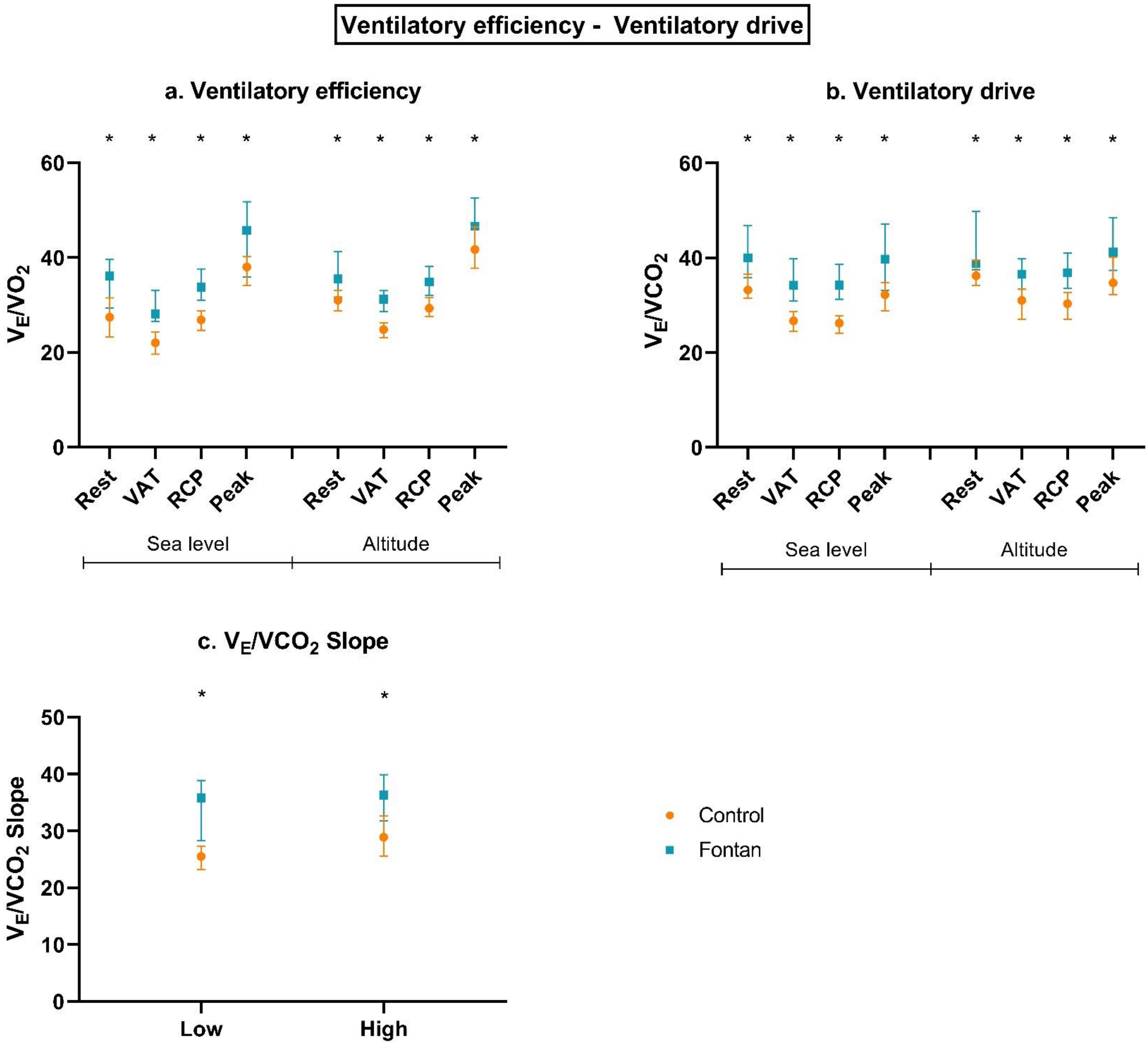
For healthy controls this ratio showed a statistically significant increase at all timepoints (Figure 3b). Between groups analysis of the V_E/Watt-ratio shows significant higher values in PwF at all time points in both conditions compared to healthy controls (Figure 3c).

Figure 1: Breathing parameters



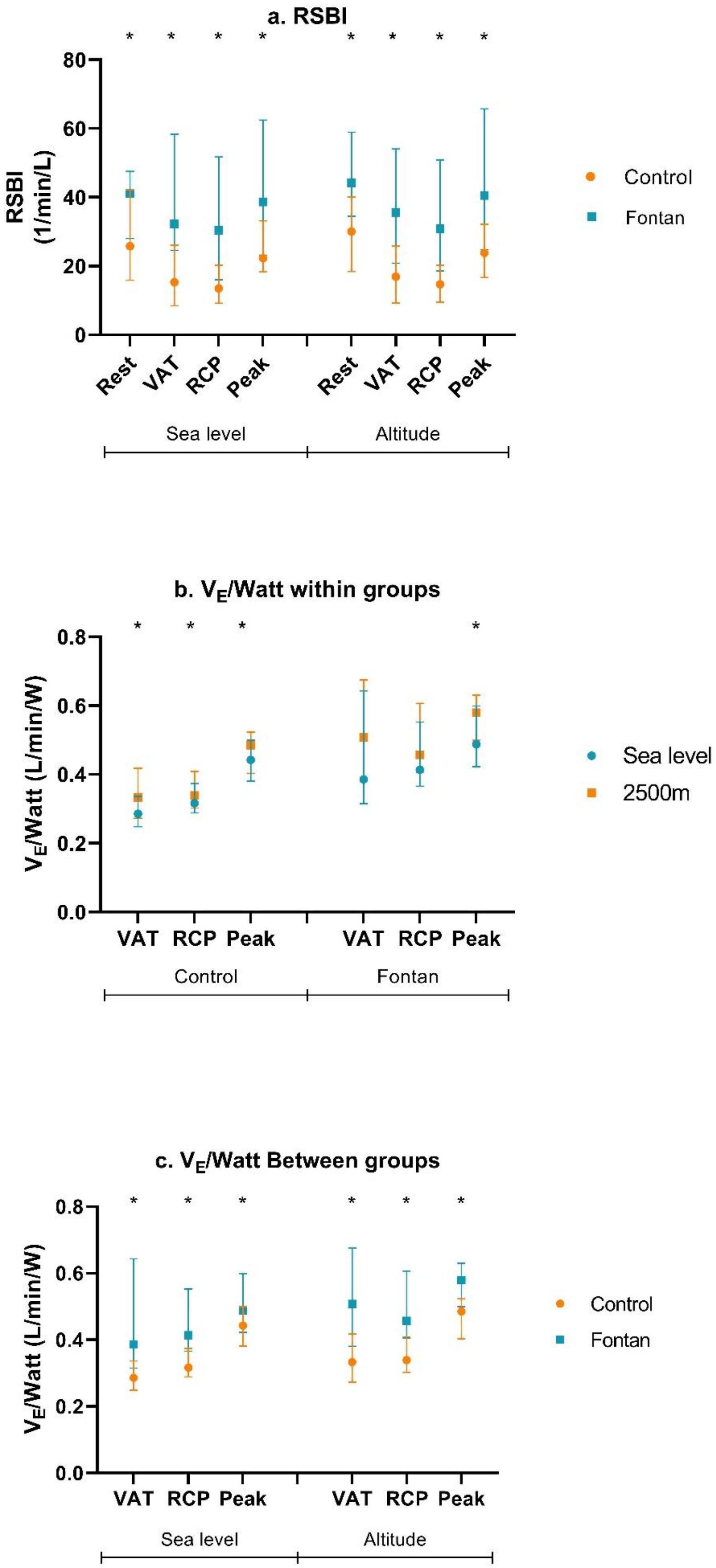
*Scores are presented as medians [interquartile range]; Comparing the groups with a two-sided Mann-Whitney U test; *= P<0.05 between groups; VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point.*

Figure 2: Ventilatory efficiency - Ventilatory drive



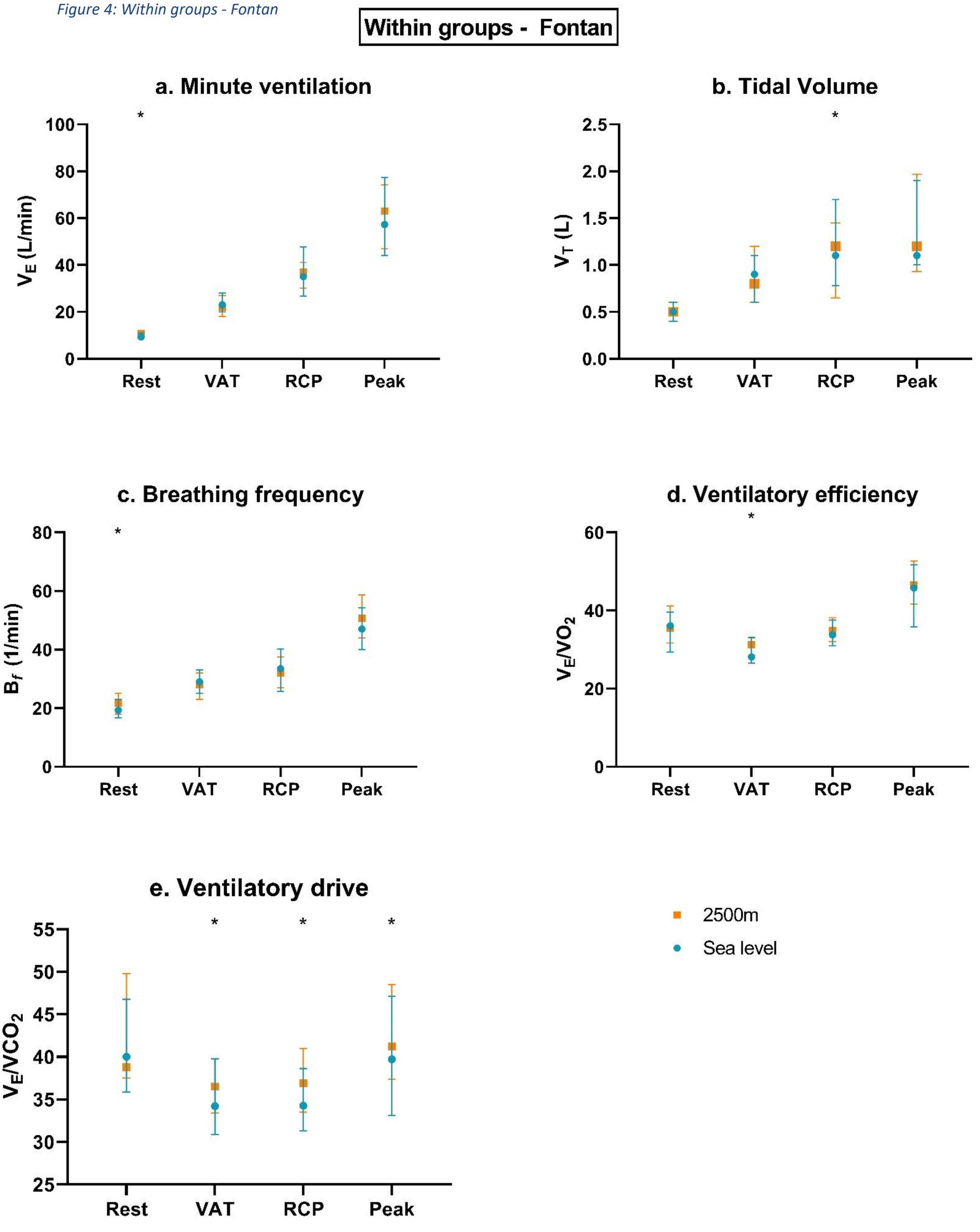
*Scores are presented as medians [interquartile range]; Comparing the groups with a two-sided Mann-Whitney U test; *= P<0.05 between groups; VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point; VE/VCO₂ -slope = The minute ventilation/carbon dioxide production slope.*

Figure 3: Rapid Shallow Breathing index and V_E/Watt



*Scores are presented as medians [interquartile range]; Comparing the groups with a two-sided Mann-Whitney U test; Comparing the conditions by a Wilcoxon signed rank test; for a-b: *= P<0.05 between groups; for c-d:*= P<0.05 between conditions; VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point;*

Figure 4: Within groups - Fontan



*Scores are presented as medians [interquartile range]; Comparing the conditions with a Wilcoxon signed ranks test; *= P<0.05 between conditions; VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point.*

4. DISCUSSION

The primary objective of this study was to investigate the effect of simulated acute normobaric hypoxia on the breathing pattern of patients with a Fontan circulation during exercise compared to a healthy control group.

Breathing patterns of PwF showed a lower increase of tidal volume than healthy controls. Resulting in a less increased respiratory minute ventilation at altitude than healthy controls. Ventilatory efficiency and ventilatory drive values were both increased. The higher minute ventilation per Watt indicates that PwF ventilate relatively more at altitude than healthy controls, indicating greater ventilatory requirements. The RSBI shows higher values at all time points. Therefore, it can be concluded that breathing patterns of PwF during exercise in hypoxia are significantly different compared to healthy controls. Where healthy controls show a hypoxic ventilatory response as described by Schoene et al. (2001) and Samuels et al. (2011), PwF show a rapid but shallow breathing pattern, making the breathing inefficient (10,13). This might explain the dyspnoea sensations of PwF when exposed to high altitude.

Compared to Staempfli et al. (2016), who studied the effects of short-term high altitude exposure on pulmonary blood flow and exercise capacity in PwF, ventilatory drive as measured by the V_E/VCO_2-slope at sea level and in hypoxia are in line with the current study (20). The V_E/VCO_2-slope showed values over 34, representing an abnormal excessive high ventilatory response to exercise (21). Which corresponds with our findings that PwF show an inefficient breathing pattern during exercise at altitude.

Although the findings correspond to previous research and the hypothesis is confirmed by the results, there are some limitations. First of all, the exposure to hypoxia in the hypoxic environment was short: participants spent on average 30 minutes in the tent. In a real hypoxic environment, there is a greater chance that people will spend days or hours rather than minutes at altitude. Second, participants in this study were tested in normobaric hypoxia. Tipton et al. (2017) reported that several studies found a greater tidal volume in normobaric hypoxia than in hypobaric hypoxia in healthy persons (12). Although different findings for breathing frequency in normobaric and hypobaric hypoxia are reported, a change in tidal volume might further influence the RSBI, resulting in an even more inefficient breathing pattern in PwF (12). Third, only PwF classified to NYHA-class I and II were recruited for this research, because there was no space to place an arm ergometer in the hypoxic tent. This makes generalizability to the entire PwF population difficult.

Although there is a great interquartile range in the tidal volume and respiratory minute ventilation of the healthy controls, at sea level and at altitude. A key strength of this study is the inclusion of children and adolescents. During childhood and adolescence, growth and developmental aspects cause differences in breathing frequency, respiratory minute ventilation and ventilatory efficiency compared to adults (22). Taking children into account is a step towards advice for high-altitude travel to the younger generation too. Further, this study simulated an altitude of 2500m. Most travelling in high altitude terrain takes place below or up to this altitude. Although breathing patterns will be more extreme when exposed to a higher altitude, outcome measures of breathing patterns on 2500m will be most useful for PwF.

With the current results, it is not possible yet to provide advice regarding safety for PwF who want to expose themselves to high altitude. This requires more specific data about breathing patterns when exposed to high altitude for a longer period. However, PwF might explore the possibilities of training their breathing technique during exercise. At sea level, respiratory muscle training in adolescent PwF resulted in improvements of inspiratory muscle strength and ventilatory efficiency during exercise (23). Respiratory muscle training is a simple technique, which has the potential to improve the exercise capacity of PwF (23,24). For healthy athletes, it is recommended to use this training as a pre-exposure tool for strengthening the respiratory muscles, thereby minimizing the adverse effects caused by hypoxia related to hyperventilation (25). To control the rapid shallow breathing, using this training as a pre-exposure tool might be a useful advice to give to PwF who wants to expose themselves to high altitude.

This is the first study to show breathing patterns in paediatric and young adults with a Fontan circulation compared to a healthy control group when exposed to hypoxia. This is only a first step to explore the effects of hypoxia on breathing patterns. Further research is needed to confirm the current results. Future research should focus on longer duration in a real altitude environment.

5. CONCLUSION

It can be concluded that PwF respond different to acute normobaric hypoxia during exercise when compared to healthy people. PwF show a more rapid shallow breathing pattern compared to healthy people, making the breath less efficient.

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